

Specification

On page 1, please replace the title with the following:

**-- A MICROELECTRONIC DEVICE FOR ELECTROCHEMICAL
DETECTION OF NUCLEIC ACID HYBRIDIZATION --**

Please delete the first two paragraphs of the specification, referred to as “first paragraph A” and “first paragraph B” on page 2 of the Official Action. Please insert the following paragraph after the title:

-- Cross-Reference to Related Applications

This application is a Divisional application of application Serial No. 09/603,217 filed June 26, 2000, now U.S. Patent No. 6,361,951, which is a Divisional application of application Serial No. 09/179,665 filed October 27, 1998, now U.S. Patent No. 6,132,971, which is a Divisional application of application Serial No. 08/667,338 filed June 20, 1996, now U.S. Patent No. 5,871,918, which in turn is a Continuation-In-Part of provisional application Serial No. 60/016,265, filed April 19, 1996 and which claims priority from application Serial No. 08/495,817, filed June 27, 1995 (converted to provisional application Serial No. 60/060,949, filed June 27, 1995), the disclosures of all of which are incorporated by reference herein in their entirety. --

Please replace the paragraph on page 5, lines 1–9 with the following:

-- **Figure 2** shows the cyclic voltammograms of $\text{Ru}(\text{bpy})_3^{2+}$ in the presence of 5'-AAATATAGTATAAAA (SEQ ID NO: 1) as a single strand (C) and hybridized to complementary strands (A & B). The scan rate is 25 mV/s. (A) represents 25 μM $\text{Ru}(\text{bpy})_3^{2+}$ + 100 μM (in guanine nucleotides) double stranded fully hybridized DNA (5'-AAATATAGTATAAAA, SEQ ID NO: 1)•(3'-TTTATATCATATTTT, SEQ ID NO: 2). (B) represents $\text{Ru}(\text{bpy})_3^{2+}$ with a duplex containing a GA mismatch (5'-AAATATAGTATAAAA, SEQ ID NO: 1)•(3'-TTTATATAATATTTT, SEQ ID NO: 3), and (C) represents $\text{Ru}(\text{bpy})_3^{2+}$ a

single strand containing one guanine nucleotide (5'-AAATATAGTATAAAA, SEQ ID NO: 1). -

Please replace the paragraph on page 5, lines 15–21 with the following:

Figure 5 shows the cyclic voltammograms of $\text{Ru}(\text{bpy})_3^{2+}$ (25 μM) at a scan rate of 25 mV/s in 50 mM sodium phosphate buffer with 0.7 M NaCl, pH 7. (A) No added oligonucleotide. (B) With 75 μM d[5'-TTTTATACTATATTT, SEQ ID NO: 2]. (C) With 75 μM of the hybrid of the oligomer from B and d[5'-GGGAAATATAGTATAAAAGGG, SEQ ID NO: 4]. Working electrode: tin-doped indium oxide. Reference electrode: Ag/AgCl. Counter electrode: Pt wire. The secondary structure of the hybrid from C is indicated on the Figure.

Please replace the paragraphs on page 6, lines 17–26 with the following:

Figure 14 shows the cyclic voltammogram of $\text{Ru}(\text{bpy})_3^{2+}$ (25 μM) alone and with (100 μM in strands) of 5'-AAATATAG_nTATAAAA (SEQ ID NO: 5) where n = 1 (G), 2 (GG), or 3 (GGG). The scan rate is 25 mV/s.

Figure 15 shows the cyclic voltammogram of $\text{Ru}(\text{bpy})_3^{2+}$ (25 μM) alone and with (100 μM in strands) of 5'-AAATAT(AGT)_nATAAAA (SEQ ID NO: 6) where n = 1, 2, or 3. The scan rate is 25 mV/s.

Figure 16 shows the cyclic voltammogram of 25 μM Ruthenium (4,4'-dimethylbipyridine)₃²⁺ (or " $\text{Ru}(4,4'\text{-Me}_2\text{-bpy})_3^{2+}$ ") alone (solid) and with (100 μM in strands) of 5'-AAATATAGTATAAAA (SEQ ID NO: 1, dotted) and 5'-AAATATAGGGTATAAAA (SEQ ID NO: 5, dashed). The scan rate is 25 mV/s.

Please replace Table 1 starting on page 37, line 18 with the following:

Table 1. Rate Constants for Oxidation of Guanine in DNA Oligomers by Ru(bpy)₃²⁺

$k(\text{M}^{-1} \text{s}^{-1})^a$	oligomer sequence	$\Delta r_{\text{Ru-G}}(\text{\AA})^b$
1.2×10^3	(5' - AAATATAGTATAAAA, <u>SEQ ID NO: 1</u>) • (3' - TTTATATCATATTTT, <u>SEQ ID NO: 2</u>) GC pair	1.7 Å
5.1×10^3	(5' - AAATATAGTATAAAA, <u>SEQ ID NO: 1</u>) • (3' - TTTATATTATATTTT, <u>SEQ ID NO: 7</u>) GT mismatch	1.2 Å
1.0×10^{4c}	(5' - AAATATAGTATAAAA, <u>SEQ ID NO: 1</u>) • (3' - TTTATATGATATTTT, <u>SEQ ID NO: 8</u>) GG mismatch	1.0 Å
1.9×10^4	(5' - AAATATAGTATAAAA, <u>SEQ ID NO: 1</u>) • (3' - TTTATATAATATTTT, <u>SEQ ID NO: 3</u>) GA mismatch	0.7 Å
1.8×10^5	(5' - AAATATAGTATAAAA, <u>SEQ ID NO: 1</u>) single strand	0 Å
5.1×10^3	(5' - AAATATAGTATAAAA, <u>SEQ ID NO: 1</u>) • (3' - TTTATATCTATTTT, <u>SEQ ID NO: 9</u>)	1.2 Å

^aDNA concentrations used to determine rate constants were based on the moles of guanine nucleotides.

^bEstimated distance of tunneling through solvent. Distances calculated according to $k/k_{ss} = \exp[-\beta\Delta r]$, where $\beta(\text{H}_2\text{O}) = 3 \text{\AA}^{-1}$ and $k_{ss} = 1.8 \times 10^5 \text{M}^{-1} \text{s}^{-1}$. ^cSince the rate constants are relative to guanine concentrations, the observed rate for the GG mismatch has been normalized relative to the other oligomers containing a single guanine.

Please enter the attached paper copy of the Sequence Listing at the end of the specification.

Attachment: paper copy of Sequence Listing